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August 17, 1998

Annie M. Jarabek
EPA - NCEA
Catawba Building
3210 Highway 54
Research Triangle Park, NC 27709

Re: Study of health effects from occupational exposure to perchlorate at Kerr-McGee's Henderson Nevada facilty

Dear Ms Jarabek:

We have completed the study that I presented in Anaheim, California last June. In addition to looking for cross-shift or chronic exposure related thyroid effects, we looked for chronic exposure related hematologic, renal and hepatic effects. The manuscript has now been through peer review and accepted for publication.

I am enclosing a copy of the manuscript as accepted for your use. Please be aware that the copyright now belongs to JOEM and do not distribute copies other than necessary within EPA. I will send you a galley proof as soon as it is available.

Sincerely,

John P. Gibbs, MD

Journal of
Occupational and
Environmental
Medicine

August 14, 1998

John P. Gibbs, MD
Vice President of Health Management
Corporate Medical Director
Kerr-McGee Corporation, PO Box 25861
Kerr-McGee Center
Oklahoma City, Oklahoma 73125

Re: Evaluation of a Population with Occupational Exposure to Airborne Ammonium Perchlorate for Possible Acute or Chronic effects on Thyroid Function (07488)

Dear Dr. Gibbs:

I am truly sorry for causing you so much distress.

Your manuscript has been fully accepted for publication, and will be printed either in November or very soon after the new year, depending on our joint decision.

Sincerely,

Elizabeth Popper
Managing Editor

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EVALUATION OF A POPULATION WITH OCCUPATIONAL EXPOSURE TO AIRBORNE AMMONIUM PERCHLORATE FOR POSSIBLE ACUTE OR CHRONIC EFFECTS ON THYROID FUNCTION

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25 pages, 5,600 words

4 figures, 7 tables

Copy #1 Annie Jarabek

ABSTRACT

Employees at an ammonium perchlorate (AP) production facility in Nevada and a larger control population from the same chemical complex without direct AP exposure were monitored extensively for airborne perchlorate exposure. Single shift and working lifetime cumulative dose estimates were made using standard breathing rate estimates and assuming rapid absorption based upon solubility. Calculated single shift doses ranged from 0.2 to 436 μg/kg with an average of 36 μg/kg. Working lifetime cumulative doses in the higher exposure group ranged from 8,000 to 88,000 μg/kg with an average of 38,000 μg/kg. Thyroid profiles including free thyroxine index (FTI) and thyroid stimulating hormone (TSH) were obtained both pre-shift and post-shift to assess thyroid axis perturbation due to single working shift perchlorate exposure. Thyroid function data were also analyzed with respect to estimates of cumulative exposure to assess any measurable chronic effects on thyroid gland function. Additionally, standard clinical blood test parameters of liver, kidney, and bone marrow function were evaluated to assess any measurable chronic effects of perchlorate exposure on those organs. Multiple regression was used to assess effects of exposure variables and demographic variables on organ function parameters. No perchlorate attributable effects on thyroid, bone marrow, kidney, or liver function were detected.

INTRODUCTION

Ammonium Perchlorate (AP) has been used as an oxidizer component in solid propellant for rockets, missiles, and fireworks for over 50 years. AP is very soluble in water where it dissociates into its component ions and can persist for many decades under typical ground and surface water conditions. Most of the United States' AP production over the past half century has been at two separate facilities near Las Vegas, Nevada due to the high electricity and low humidity requirements for the process and storage of AP.

Recent (April 1997) advances in the analytical detection capability for low concentrations of perchlorate have resulted in the lowering of the reporting threshold from 400 down to 4 parts per billion (ppb). As a result, perchlorate has been discovered in ground water near various manufacturing sites in California, Nevada, and Utah. Perchlorate has also been detected at ppb levels in Lake Mead and in the Colorado River downstream from Lake Mead, which together serve as a drinking water source for approximately 20 million people in Nevada, Arizona, and Southern California

Our knowledge of the health effects of perchlorate in humans derives primarily from studies and reports on patients with Graves' disease. Potassium perchlorate was widely used in the treatment of hyperthyroidism during the 1950's and early 1960's. The perchlorate ion readily absorbs systemically from the GI tract. Its physiological effect is to reversibly inhibit iodide uptake in the

thyroid, thereby lowering thyroid hormone levels and controlling the symptoms of hyperthyroidism. Alterations in thyroid function are thought to be the most sensitive potential effect from low level environmental contamination. Perchlorate is excreted unchanged by the kidneys with a half life of approximately 6 hours[29].

Studies of perchlorate in Graves' patients range in duration from a single dose[1] to several weeks [2,3,4,,5,6,7,8,9,10]. One case study[11] reports treatment with perchlorate in a single patient for 22 years. Doses of perchlorate range from < 1 mg/kg-day[1] to > 20 mg/kg-day[3] with typical doses in the range of 6-14 mg/kg-day. Effects observed include the blockage of iodide uptake and iodide discharge by thyroid[1], gastrointestinal irritation, skin rash[2,3], and hematological effects including agranulocytosis and lymphadenopathy[3,5]. Seven cases of fatal aplastic anemia were reported during the period 1961 - 1966 at doses of 6-14 mg/kg-day[4,6,7,8,9,10].

Two studies examined the effects of perchlorate in healthy volunteers. Burgi et al[12] studied perchlorate at 9.7 mg/kg-day on five subjects for eight days and Brabant et al[13] studied perchlorate at 12 mg/kg-day on five subjects for four weeks. Both studies observed effects on the thyroid at these doses.

Perchlorate is currently used in several European countries to prevent hyperthyroid side effects from an antiarrhythmic cardiovascular drug, amioderone. Patients are typically treated with doses up to 14 mg/kg-day and usage in this context has not been reported to result in aplastic anemia.

Perchlorate is still available in the US for administration (200-400 mg given by mouth) ½ to 1 hour prior to the administration of $NaTcO_4$ for brain, blood pool imaging, and placenta localization. Perchlorate ions block the uptake of $^{99}TcO_4^-$ ions in the choroid plexus, salivary, and thyroid glands.

Employees at the two AP facilities in the US have been exposed historically to perchlorate occupationally through the respiratory, and possibly through the oral routes. Significant absorption of perchlorate through intact skin is unlikely; however significant systemic absorption of inhaled perchlorate through mucous membranes in the respiratory and GI tracts is likely due to its high aqueous solubility at body temperature.

No specific OSHA standard for perchlorate exists, and it has been categorized as a nuisance dust with an 8 hour time weighted average permissible exposure limit of 15 mg/m^3. Safety concerns due to explosion potential have been considered to outweigh any risk of pharmacologic effect from exposure. In 1988 one of the two facilities near Las Vegas blew up and was subsequently rebuilt in Utah. Commercial production of AP was discontinued in June, 1998 at the facility near Las Vegas which left the Utah plant as the only production facility in the U.S..

This study was started in September 1997 to determine the levels of perchlorate exposure, both acute and chronic, among workers at the ammonium perchlorate production facility near Las Vegas and to determine if there are any

measurable adverse effects on thyroid, bone marrow, kidney, or liver function using routine clinical blood tests. New exposure and biological monitoring data were obtained and analyzed in conjunction with previously obtained medical surveillance data at the facility.

METHODS

STUDY TIMELINE

This study was carried out at an AP production facility and an associated AP crossblending facility near Las Vegas. A medical surveillance program was started at those facilities in 1994 that included a blood test (CBC and serum chemistries), a medical history, and a physician examination. For 12 months starting in early January 1996, a thyroid panel was added to the blood test. In early 1997, evaluation of the 170 thyroid tests obtained in 1996 did not indicate any difference between perchlorate exposed employees and those without exposure; however no exposure estimates were available.

In September 1997, a campaign was initiated to obtain pre-shift and post-shift thyroid profiles on as many employees as possible, both exposed and non exposed (all voluntary) and to fully characterize exposures. In all, 133 employees volunteered for pre-shift and post-shift blood tests and 24 full shift breathing zone exposure measurements (with detectable levels of AP)were made. In March 1998, another campaign was initiated to measure worker exposures using a much more sensitive analytic method. This time 95 full-shift personal breathing zone exposure measurements and 25 full-shift area

exposure measurements were made. In addition, 16 more pre-shift and post-shift blood tests were obtained on the more highly exposed employees during this same time period. In October 1997, the sale of the AP business was announced and commercial production of AP at the facility ceased in June 1998.

EXPOSURE ASSESSMENT

Breathing Zone Personal Sampling Methods: Full shift sampling was carried out under the direction of a certified industrial hygienist using 5 μm polyvinyl chloride filters in 37mm closed-face cassettes. Air was sampled at a rate of 2.0 liters per minute using standard industrial hygiene sampling pumps which were calibrated daily.

Analytical Methods:

The September 1997 laboratory analysis of the filter cassettes, based on quantification of ammonium ion using NIOSH method 6016 (LabCorp Analytics) had a minimum reporting limit of approximately 17 μg/ M^3. The March 1998, analysis carried out at Montgomery Watson Laboratory in Pasadena, California using 300.0 modified EPA methodology (ClO_4^- determination using ion chromatography) had a minimum reporting limit of approximately 0.04 μg/ M^3. With this method perchlorate was detectable in all plant areas and in many offices of employees who frequented the AP process areas whereas with the September 1997 analysis a large percentage of the samples were reported as non detectable. Exposure levels in the dustier areas of the facility appeared to compare quite well.

EXPOSURE GROUPS:

Eight homogeneous exposure groups were defined based upon similar job activities and exposure potential. These included a control group who were never in the production areas, maintenance workers and foremen who were casually in the production areas and six discrete operator job categories. Multiple samples were taken for each of these groups (total of 119 personal breathing zone samples) to determine the distribution of exposures for that group. For the control employees working in non AP other areas of the plant, exposures were estimated using the 19 full shift area samples that were collected in areas of the plant where the majority of the control employees worked.

Employees in one of the dustiest homogeneous exposure group routinely wore respirators during the dustier job cycles. When a respirator was used intermittently during the dustier activities, the exposure concentration was adjusted downward by 65% based upon two full day assessments when the industrial hygienist changed filter cassettes every time the employee put a respirator on or took it off.

DOSE ESTIMATION:

Dose was estimated by:

[respiratory rate] x [inhalation concentration] x [exposure duration] x [fraction absorbed]

Respiratory rates of 0.0068 M^3/Kg-hr and 0.0165 M^3/Kg-hr were estimated for sedentary and active workers respectively based on work by Beals et al[14]. Active workers in this study were assumed to perform work in the "moderate" category from Beals et al, which included walking 2-3 mph, woodworking, yard work, house work, and car repair, while sedentary workers were presumed to perform work characterized by the "low" activity group. Average weights of 89 Kg and 74 Kg respectively for men and women were used based upon company medical records. Daily respiration volumes for an active 70 Kg worker are thus 9.2 M^3 over an 8 hour shift and 13.9 M^3 over a 12 hour shift.

The estimated fraction absorbed is based on work by Boecker[15] with CsCl in beagles. That study indicated that, on average, 78% of inspired CsCl aerosol (based on breathing rates and average air concentrations) was retained initially in the animals. Due to its high aqueous solubility at body temperature, it was assumed that AP is similarly absorbed.

Single shift dose estimates: The exposure duration was taken as the time elapsed between the preshift and postshift blood tests. The exposure concentration was directly measured for that shift.

Working lifetime dose estimates: Personnel records were reviewed and employees were interviewed to determine the number of years worked in each of the seven homogeneous exposure groups. An average of 2,000 hours worked yearly was assumed based upon typical overtime rates at the facilities. Each subject's working lifetime cumulative dose was then estimated as:

$$\sum [\text{mean group exposure}] \times [\text{years in exposure group}] \times 2{,}000$$

BIOLOGICAL ENDPOINTS:

Thyroid function : The standard clinical thyroid profiles included a total serum thyroxine (T4) , triiodothyronine resin uptake (T3U), and an ultra sensitive Thyroid Stimulating Hormone (TSH) assay. The free T4 index (FTI), calculated as the product of the T4 and T3U, is considered the best estimate of free T4. Two different clinical reference laboratories were used in this study. LabCorp (Kansas City) was used for the 1996 thyroid profiles at the time of routine medical surveillance exams. Associated Pathologists Labs (Las Vegas) was used during 1997 - 1998 for thyroid blood tests collected pre and post shfit. This selection was made primarily due to the laboratory's close proximity to the production facility.

Bone marrow function: Standard tests from the complete blood count (CBC) obtained during medical surveillance examinations in 1996, 1997, and 1998 were used to assess hematopoetic function. These included the hemoglobin level (HGB), hematocrit (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), and platelet count. All tests were performed by LabCorp in Kansas City.

Kidney and liver function: Standard serum chemistries obtained during medical surveillance examinations in 1996, 1997, and 1998 were used to assess kidney and liver function. Tests of kidney function included serum creatinine level and

blood urea nitrogen (BUN) level. Tests of liver function included serum glutamyl pyruvic transaminase (SGPT), serum glutamyl oxaloacetic transaminase (SGOT), g-glutamyl transpeptidase (GGTP), and alkaline phosphatase. All tests were performed by LabCorp in Kansas City.

STUDY DESIGNS

The single shift thyroid effects study was designed to detect any measurable transient effects on the thyroid axis due to exposure on a single day. Participation in this study was voluntary on the part of the employees. Employees taking thyroid medications were intentionally not discouraged from volunteering for blood tests in order to protect their medical confidentiality and to encourage honest self reporting of thyroid medication status. Nominal rewards were offered to encourage participation. All employee exposure days (24 exposure days on 18 different individual employees) were identified during which breathing zone exposure monitoring was conducted on the same day that the individual volunteered for pre-shift and post-shift blood thyroid tests.

All employees who volunteered for blood tests in 1997 and 1998 completed a one page questionnaire indicating whether or not they had had worked in the AP process area in the preceding 30 days, how much they had slept in their last sleep period, and when they had awoken. The time of day that each blood sample was taken was recorded . For each of the exposed group, a shift dose estimate was made based upon exposure monitoring for that specific shift and the elapsed time between the pre-shift and post-shift blood tests. For this study, the control group (92 employees) was selected from all employees who

volunteered for pre-shift and post-shift thyroid function tests and who indicated that they had not worked in an AP area in the preceding 30 days. Nine employees who indicated that they were taking or had ever been advised to take thyroid medication were excluded from either group for statistical analysis (all controls, reducing the control group to 83). Thirty employees with a history of exposure within the preceding 30 days but who were not monitored during the specific shift that the blood tests were taken were also excluded from statistical analysis (but were included in the working lifetime study).

Working lifetime thyroid effects study. Of the 254 employees at the plant, 170 employees had a thyroid function test with their medical surveillance examination in 1996. In addition 130 employees (294 blood tests) volunteered for pre-shift and post-shift thyroid studies in 1997 and 1998. Employees who had never worked in any jobs with AP exposure based upon personnel records were identified as the control group and dose estimates were made based upon area monitoring for perchlorate and job type (sedentary or active). Cumulative dose estimates were made for the remainder of the employees for whom thyroid function data existed. The exposed group arbitrarily stratified into a high cumulative dose group (> 8,000μg/kg) and a low cumulative dose group (< 8,000 μg/kg). As with the single effects study, any employees indicating that they were taking or had been advised to take thyroid medication were excluded (9 controls, 2 from the high dose group). Medical records were reviewed and employees questioned if either the TSH or FTI was more than 3 standard deviations from the mean to assure the lack of a known clinical diagnosis.

Working lifetime kidney, liver, and bone marrow function study: Using the group defined for the working lifetime thyroid effects study, all routine blood tests from medical surveillance exams in 1996, 1997 and 1998 were identified. Standard tests on the blood panel were selected as indicative bone marrow, kidney, or liver function. Working lifetime perchlorate doses were estimated for the date that each blood sample was collected.

STATISTICAL METHODS

Multiple regression was used to study the relationships between measures of thyroid function, bone marrow function, liver function or kidney function and various potential explanatory variables. A sequential approach was used to determine whether a dependent variable would be log-transformed and whether any outliers would be eliminated from an analysis. First, an ordinary multiple regression was applied to all of the data using the untransformed dependent variable. If the residuals from this regression were significantly non-normal ($p < 0.05$) by the Wilk-Shapiro test[16] the regression was repeated using the log-transform of the dependent variable. If these residuals were found to be significantly non-normal, the regression using the untransformed variable was repeated with outliers omitted. (An outlier was defined statistically as a value whose corresponding residual was larger in absolute value than three standard deviations.) Finally, if these residuals were found to be non-normal, the regression was repeated using the log-transformed independent variable and with outliers eliminated. (However, log-transforms were not considered in analyses of the single shift study.) The multiple regression reported herein was from the data

set for which residuals were found to be satisfactorily normally distributed ($p > 0.05$).

Once a data set with normally distributed residuals was obtained, a regression was performed that took account of the fact that multiple measurements were made on the same subject. This regression was conducted using the MIXED procedure in SAS, and permitted multiple measurements on the same individual to be correlated.

The dependent variables evaluated in the single shift study were the cross-shift change (post-shift minus pre-shift) in measures of thyroid function, T3U,T4, FTI and TSH. The non-perchlorate explanatory variables used in the acute study were race, gender, age, hours awake prior to pre-shift test, number of hours slept during the most recent period of sleep prior to testing, time of day (indicator of whether or not pre-shift test was conducted between 6 AM and 6 PM) and shift length (8 or 12 hours). The perchlorate variable used was the single shift exposure estimate in μg/kg-day.

The dependent variables evaluated in the working lifetime study were measures of thyroid function (T3, T4, FTI, TSH), measures of hematological function (HGB, HCT, RBC, MCV, WBC, platelets), measures of liver function (SGOT< SGPT, GGTP, alkaline phosphatase) and measures of kidney function (BUN, creatinine). The non-perchlorate explanatory variables used in the working lifetime study were age, gender, and race. For thyroid tests, an additional explanatory variable was added to indicate whether the measurement was from a routine physical

examination in 1996, for a pre-shift examination in 1997-98, or a post-shift examination in 1997-98. The perchlorate dose variables used were group (control, low dose or high dose) and estimated total working lifetime cumulative perchlorate dose in μg/kg. The group variable and estimated total working lifetime perchlorate dose were not both used in the same analysis; rather the analyses described above were conducted twice, once using a group variable, and once using the estimated total dose variable.

Contingency table analyses (SAS, 1989) were performed to evaluate whether the percentage of individuals were elevated TSH, low FTI, low HGB, low WBC or low platelet count (defined as out of the normal ranges for these endpoints provided by the laboratories) was different among controls, low exposure and high exposure groups. These analyses were performed both using individual test results as the basic sampling unit (ignoring the fact that multiple tests were performed on the same individual), and using individuals as the basic sampling unit by assigning an individual the common result of multiple tests when all tests on the individual were in agreement, and eliminating individuals (no more than five in any analysis) whose test results were not in agreement.

RESULTS

EXPOSURE CHARACTERIZATION FOR HOMOGENEOUS EXPOSURE GROUPS

A summary of the exposure characterization for the eight homogeneous exposure groups is presented in Table 1. Although the controls exposure was

non zero, it was several orders of magnitude lower than that of the exposed groups. Maintenance and first line supervisors who were casually in the area were grouped together and had significantly lower exposure than all but one of the operations jobs. The measured exposures in this table do not account for occasional respirator use.

SINGLE SHIFT STUDY

Results from the single shift study are presented in Tables 2, 3 and 4 and in Figures 1 and 2. Residuals were normally distributed (p>= .05) in each case. As shown in Table 2 exposures were monitored on a total of 18 different workers (24 separate shifts) on shifts that the worker volunteered for pre-shift and post-shift blood tests. Estimated doses ranged from 0.2 - 436 μg/kg-day with a mean and median of 36 and 13 μg/kg -day respectively. Table 3 demonstrates that exposure (dose estimate) was not a significant predictor of the cross shift change in any of the thyroid parameters (p-values ranged from 0.52 to 0.94). The only significant finding was that cross-shift TSH changes was greater for those who worked 12 hour shifts than for those who worked 8 hour shifts.

Of the exposed group, 25% worked 8 hour shifts and 75% worked 12 hour shifts, while 76% of the controls worked 8 hour shifts and 24% worked 12 hour shifts. The cross-shift TSH difference correlated strongly with shift duration (p=.01) with the 12 hour shift accounting in a 0.45 UIU/ml increase across the shift. Table 4 details the cross-shift difference in TSH by group and by shift duration. No other statistically significant correlations were detected in cross-shift changes in thyroid parameters and explanatory variables tested.

WORKING LIFETIME STUDY

Results from the working lifetime study are presented in Tables 5-7 and in Figures 3 and 4. Residuals were reasonably normally distributed (p>= .04) except for SGPT (p=.0008). As shown in Tables 5 and 6, working lifetime perchlorate dose estimates ranged from 500 to 7,000 (mean = 3,500) μg/kg for the low dose group and from 8,000 to 88,000 (mean = 38,000) μg/kg for the high dose group. Tenure for the two exposure groups combined ranged from 1 to 27 years (mean=8.3).

As shown in Table 7 no significant correlations with estimated lifetime cumulative perchlorate dose were detected in any of the measures of thyroid, bone marrow, liver, or kidney function. Using the stratified groups in the regression analyses, the white blood cell count was higher for the low dose group than for the control or high dose groups (p=.04). No other significant group effects were detected. Thyroid tests appeared to differ statistically between the two reference laboratories used but no age or gender associations were noted for TSH or FTI.

Statistically significant gender and race differences were apparent in the clinical tests of bone marrow function, liver function, and kidney function. Hemoglobin, hematocrit, SGPT, GGTP, and creatinine were all slightly lower in females relative to males. Black workers had slightly lower hemoglobin and hematocrit values and slightly higher creatinine levels relative to white workers.

A separate analysis was performed to evaluate the number of blood tests and individuals with an elevated TSH, low FTI, low HGB, low WBC or low platelet count in each group. No exposure attributable effect of perchlorate was apparent when looking for these specific abnormalities.

DISCUSSION

The data presented in this report show clearly that at the inhalation exposure levels typical at the Henderson AP facility, there was no observable trend toward thyroid, bone marrow, kidney, or liver toxicity as measured with routine clinical blood tests. The correlation of shift duration with cross-shift change in TSH is consistent with published reports of circadian changes in serum TSH levels[17,18,19]. The majority of employees started their shift within 1-4 hours of awakening. The end of an 8 hour shift would coincide with the end of the plateau in TSH levels prior to the evening rise in levels. The end of a 12 hour shift would coincide with a period when TSH has started to rise or has been rising for a few hours.

Average single shift exposures in this study were 36 μg/kg-day while the maximum single shift exposure was 436 μg/kg day, equivalent to 0.4% and 4% respectively of the daily dose that was typical in the treatment of Graves disease (6,000 - 14,000 μg/kg-day). Average working lifetime cumulative doses

for the high and low dose groups were 38,000 µg/kg and 3,500 µg/kg respectively over an average 8.3 year period of time. These average working lifetime cumulative doses are equivalent to ½ and 5 times the daily dose typically given for Graves disease for the low and high dose groups respectively. The highest cumulative perchlorate dose in this study (88,000 µg/kg over 10 years) is equivalent to the cumulative dose typically prescribed in the treatment of Graves disease over approximately two weeks.

The concern being addressed in this study, however, is that of low level exposure through drinking water, not exposures through the respiratory route. At this time, there are no reports in the literature specifically on the absorption of perchlorate salts through the respiratory route in humans or in animals. Principles of chemistry and physiology along with limited data on AP and other soluble salts strongly support the assumption made in this report that the majority of inhaled perchlorate was absorbed.

The exposure of concern is the perchlorate ion and not the particular perchlorate salt. Perchlorate salts dissociate completely when dissolved in water or aqueous tissues. The solubility of ammonium perchlorate in water at body temperature is approximately the same as that of sodium chloride. One would expect that inhaled AP would rapidly dissolve on moist mucous membranes in the nose, throat, mouth or lungs except for a small fraction that could be inhaled and exhaled without contacting a moist mucous membrane.

In humans, approximately 50% of 10μ particulates are deposited in the mouth and throat and 50% are deposited in the bronchial, bronchiolar or alveolar region of the lung[20]. Particulates less than 10μ are deposited relatively more in the lung regions while particulates greater than 10μ are deposited relatively more in the mouth and throat. Particulates that are deposited in the mouth and throat as well as many of those depositing in the trachea and brohchi will be presented to the GI tract for absorption (thus directly comparable to AP in drinking water). Since perchlorate ion is excreted unchanged in the urine, it is unlikely that there is any first-pass effect on absorbed perchlorate in the liver, gut, or lung.

Studies[21,22,23,24] in beagles in the 1960's using $^{137}CsCl$, a highly soluble radioactive salt, supports the assumption that AP is rapidly absorbed systemically through respiratory exposure. Calculations using measurements of the air volumes inspired and mean exposure ^{137}Cs air concentrations indicated that an average of 78% (69-87%) of the total inspired ^{137}Cs was deposited initially in these animals. The metabolism and dosimetry of ^{137}Cs was shown to be similar for the inhalation and intravenous routes of dosing. There was rapid translocation of inhaled ^{137}Cs to other tissues so that ^{137}Cs in the lung became one of the lowest tissues analyzed. Because the ^{137}Cs was rather uniformly distributed throughout the body, the whole body was considered the critical organ for dosimetry purposes.

Thyroid disorders are relatively common in the general population[24,25,26,27,28,29] and increase with age with females typically having a higher prevalence than males. Due to the difference in age groups of study populations and differences in definitions of hypothyroidism and hyperthyroidism it is difficult to compare the prevalence of these diseases in our study with other US studies. Comparison with one study (Remedios et al[27]) , however, is possible. They selected a group of 2,606 adults without known history of thyroid disease from northern California and stratified the group by FTI. 87% of their population had a FTI between 1.41 and 3.40, while in our study none of the controls or exposed were below 1.06 or above 3.70 and 96.4% of our population were between 1.41 and 3.40. Age and gender were not found to correlate significantly with indices of thyroid function, however, the number of females in our study was relatively low (17%) and the age range relatively narrow (mean = 43.8, std dev = 9.4).

CONCLUSIONS

Calculated perchlorate doses from occupational exposures to airborne AP dust during the manufacture and crossblending of AP are two to three orders of magnitude less than doses historically prescribed in the treatment of Graves disease. These same doses are two to three orders of magnitude greater than would result from consumption of drinking water from Lake Mead or the Colorado River. Calculated working lifetime cumulative dose over an average of 8.3 years is up to 10 times the cumulative dose that would result from drinking

water from Lake Mead or the Colorado River for a lifetime. No exposure related effects on thyroid gland function (either acute or chronic) and no chronic exposure related effects on bone marrow, liver, or kidney function were found.

ACKNOWLEGEMENTS

The authors would like to thank Dr. Joan Dollarhide and Dr. Michael Dourson and Dr. Steven Lamm for their encouragement and advice on this study and Dr. Roger McClellan at CIIT for his assistance in finding references documenting the absorption and distribution of airborne soluble salts. We wish to thank the Employee Relations Department at the Kerr-McGee Henderson facility for scheduling tests and for their work in reviewing personnel records for work history. Lastly, we would like to thank the employees of Kerr-McGee Chemical LLC in Henderson and Apex, Nevada for their co-operation with this study, without which this study would not have been possible.

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Table 1 EXPOSURE CHARACTERIZATION OF HOMOGENEOUS EXPOSURE GROUPS
(all exposures in ug perchlorate/M3)

	N	AVG	STD	MIN	P25	MED	P75	MAX
Controls	19	0.036	0.052	0.000	0.000	0.018	0.036	0.194
Maint & Foremen	25	23.6	28.1	1.2	5.2	9.6	31.3	104.3
Operations job #1	10	20.6	27.1	2.4	4.4	6.8	26.8	94.0
Operations job #2	11	369.0	776.5	6.4	29.3	40.5	208.3	2,740.7
Operations job #3	14	92.4	54.0	18.2	52.0	73.1	130.5	183.9
Operations job #4	13	267.4	284.6	29.6	63.3	169.3	336.8	971.6
Operations job #5*	32	614.6	813.1	20.6	81.6	313.3	625.8	3,350.0
Operations job #6	14	627.0	759.0	62.7	178.1	383.8	655.5	3,070.0

* respirators routinely worn on job #5 for the dustier operations

TABLE 2 THYROID FUNCTION TESTS FROM SINGLE SHIFT STUDY

						PRE-SHIFT				POST-SHIFT			
		DOSE EST	AGE	TENURE	TIME*	T3U	T4	FTI	TSH	T3U	T4	FTI	TSH
CONTROLS													
83 TESTS	AVG	--	44.9	12.5	8.6	29.3	7.5	2.1	2.2	29.0	7.5	2.1	2.2
83 INDIVIDUALS	STD	--	9.2	8.5	1.5	3.5	1.8	0.4	1.2	4.4	1.8	0.4	1.1
65 MALE, 18 FEMALE	SEM	--	1.0	0.9	0.2	0.4	0.2	0.0	0.1	0.5	0.2	0.0	0.1
63 8HR SHIFTS	P25	--	38.1	5.7	7.8	27.4	6.4	1.9	1.5	26.8	6.6	1.9	1.4
20 12 HR SHIFTS	MED	--	44.4	10.9	8.2	29.1	7.3	2.2	2.1	28.8	7.3	2.2	2.0
	P75	--	51.1	17.7	8.9	31.8	8.3	2.4	2.8	30.9	8.2	2.4	2.7
EXPOSED													
24 TESTS	AVG	36.2	41.2	9.3	10.2	29.8	7.0	2.1	2.2	29.4	7.3	2.1	2.5
18 INDIVIDUALS	STD	85.2	10.1	7.2	2.4	2.0	1.4	0.5	1.2	2.2	1.2	0.4	1.5
15 MALE, 3 FEMALE	SEM	17.4	2.1	1.5	0.5	0.4	0.3	0.1	0.3	0.5	0.2	0.1	0.3
6 8HR SHIFTS	P25	6.7	32.9	3.9	9.1	28.4	6.0	1.8	1.5	28.5	6.2	1.8	1.7
18 12HR SHIFTS	MED	13.3	37.2	6.7	11.3	29.3	7.0	2.1	2.0	29.1	7.5	2.2	2.1
	P75	35.7	49.1	12.3	11.8	30.7	8.2	2.4	2.5	31.4	8.2	2.4	3.3

* hours between pre-shift and post-shift blood tests (>9 hrs = 12 hr shift)

TABLE 3

MULTIPLE REGRESSION p-VALUES FROM SINGLE SHIFT STUDY

	CROSS SHIFT CHANGE			
	T3U	T4	FTI	TSH
DOSE ESTIMATE	0.83	0.88	0.94	0.52
AGE	0.84	0.80	0.80	0.75
GENDER	0.30	0.38	0.95	0.46
RACE	0.25	0.83	0.43	0.06
HRS SLEEP	0.45	0.32	0.43	0.85
HRS AWAKE	0.49	0.44	0.44	0.36
SHIFT TIME	0.20	0.31	0.59	0.18
SHIFT DURATION	0.36	0.51	0.46	**0.01**

HRS SLEEP = reported hours slept during last sleep period

HRS AWAKE = hours awake before starting shift

SHIFT TIME stratified into 6AM-6PM or 6PM-6AM at start of shift

SHIFT DURATION = 8hrs or 12hrs

TABLE 4
ANALYSIS OF CROSS-SHIFT TSH CHANGE

	CONTROLS	EXPOSED
12 HOUR SHIFTS	N=20 AVG=+.25	N=18 AVG=+.38
8 HOUR SHIFTS	N=63 AVG=-.13	N=6 AVG=+.12

TABLE 5 THYROID FUNCTION TESTS FROM WORKING LIFETIME STUDY

'96 EXAMS - LABCORP		DOSE	AGE	TENURE	T3U	T4	FTI	TSH
CONTROLS								
120 TESTS	AVG	75	43.7	10.6	32.0	8.14	2.54	2.25
120 INDIVIDUALS	STD	59	10.0	7.8	3.4	1.43	0.44	1.76
101 MALE, 19 FEMALE	SEM	5	0.9	0.7	0.3	0.13	0.04	0.16
	P25	23	36.9	4.1	30.0	7.20	2.20	1.40
	MED	64	42.8	9.2	32.0	8.10	2.60	1.82
	P75	114	51.6	16.3	34.0	9.10	2.80	2.59
LOW DOSE								
26 TESTS	AVG	3,369	44.3	5.8	32.1	8.26	2.58	1.81
26 INDIVIDUALS	STD	1,771	8.1	3.7	2.7	1.41	0.41	0.71
20 MALE, 6 FEMALE	SEM	347	1.6	0.7	0.5	0.28	0.08	0.14
	P25	2,037	39.3	2.8	30.0	7.30	2.25	1.40
	MED	3,323	43.3	5.6	32.0	8.15	2.55	1.92
	P75	4,048	49.0	7.6	34.0	9.28	2.88	2.16
HIGH DOSE								
22 TESTS	AVG	28,629	39.9	8.8	31.9	8.07	2.35	2.34
22 INDIVIDUALS	STD	21,038	7.2	5.7	4.8	2.09	0.68	2.51
19 MALE, 3 FEMALE	SEM	4,485	1.5	1.2	1.0	0.44	0.14	0.53
	P25	10,732	34.3	4.3	31.0	6.73	2.13	1.32
	MED	20,723	39.7	7.7	32.0	7.75	2.35	1.64
	P75	41,562	46.3	11.9	34.0	8.88	2.78	2.27
'97-98 STUDY - ASSOCIATED PATHOLOGISTS LABORATORIES								
CONTROLS								
150 TESTS	AVG	93	45.7	14.0	29.3	7.54	2.17	2.25
72 INDIVIDUALS	STD	65	9.9	9.1	3.5	1.64	0.35	1.28
60 MALE, 12 FEMALE	SEM	5	0.8	0.7	0.3	0.13	0.03	0.10
	P25	38	38.3	6.8	27.2	6.60	1.95	1.40
	MED	96	44.4	14.4	28.9	7.40	2.20	1.90
	P75	131	53.6	18.9	31.8	8.28	2.43	2.70
LOW DOSE								
40 TESTS	AVG	3,649	46.9	7.3	28.3	7.87	2.22	2.54
18 INDIVIDUALS	STD	1,661	6.5	3.6	2.0	1.47	0.41	0.93
13 MALE, 5 FEMALE	SEM	41	2.6	1.9	1.4	1.21	0.64	0.96
	P25	2,470	41.8	4.9	27.4	6.65	1.94	1.90
	MED	3,409	45.5	7.1	28.3	8.20	2.28	2.50
	P75	4,504	50.9	9.3	29.2	8.85	2.47	3.10
HIGH DOSE								
86 TESTS	AVG	40,773	40.1	9.5	30.1	7.23	2.15	2.26
31 INDIVIDUALS	STD	23,263	8.2	6.0	4.0	1.60	0.47	1.70
27 MALE, 4 FEMALE	SEM	2,509	0.9	0.6	0.4	0.17	0.05	0.18
	P25	23,405	34.9	4.6	28.5	6.13	1.81	1.33
	MED	37,256	37.5	8.6	29.5	6.85	2.15	1.85
	P75	59,612	48.3	12.4	31.6	8.28	2.41	2.60

TABLE 6

LIVER, KIDNEY AND HEMATOLOGICAL TESTS FROM WORKING LIFETIME STUDY

					LIVER				KIDNEY		BONE MARROW					
		AGE	TENURE	DOSE	SGOT	GGTP	SGPT	ALKP	BUN	CREAT	WBC	RBC	HGB	HCT	MCV	PLATS
CONTROLS																
258 TESTS	AVG	44.3	11.4	76	24.4	42.7	25.8	79.6	15.0	1.03	6.56	4.872	15.03	45.34	93.1	236.7
133 INDIVIDUALS	STD	9.57	7.9	56	13.9	102.2	12.9	26.7	3.9	0.17	1.98	0.346	1.21	3.53	4.7	49.6
112 MALE, 21 FEMALE	SEM	0.6	0.5	5	0.9	6.4	0.8	1.7	0.2	0.01	0.12	0.022	0.08	0.22	0.3	3.1
	P25	38.1	4.6	25	18.0	18.0	17.0	61.0	12.0	0.90	5.23	4.650	14.30	43.20	90.0	203.3
	MED	43.8	10.7	67	22.0	29.0	23.0	74.0	15.0	1.00	6.20	4.890	15.10	45.20	93.0	232.0
	P75	51.5	16.7	114	27.8	42.8	30.0	94.8	18.0	1.10	7.40	5.100	15.80	47.80	96.0	262.0
LOW DOSE																
68 TESTS	AVG	45.4	6.6	3,329	24.4	33.6	27.1	83.5	14.6	1.01	7.36	4.980	15.24	46.05	92.6	223.1
27 INDIVIDUALS	STD	7.05	3.5	1,796	10.2	21.4	18.2	27.9	3.4	0.17	2.39	0.334	1.26	3.32	4.2	56.4
21 MALE, 6 FEMALE	SEM	0.94	0.5	312	1.4	2.9	2.4	3.7	0.5	0.02	0.32	0.045	0.17	0.44	0.6	7.5
	P25	40.5	3.7	2,048	18.0	17.8	16.0	65.0	12.0	0.90	5.58	4.803	14.30	43.85	90.0	175.5
	MED	44.3	6.6	3,001	21.5	28.0	21.5	77.0	14.5	1.00	6.60	5.040	15.25	45.95	93.0	229.0
	P75	50.3	8.1	4,309	27.0	41.0	33.3	93.8	17.0	1.10	8.30	5.213	16.03	48.30	95.0	265.8
HIGH DOSE																
47 TESTS	AVG	40.1	9.7	29,561	29.9	71.6	77.4	86.6	15.7	1.04	6.54	4.965	15.01	45.21	91.2	229.9
25 INDIVIDUALS	STD	7.62	5.8	21,417	36.7	207.4	332.5	58.5	4.5	0.20	1.91	0.356	0.90	2.75	3.9	52.2
22 MALE, 3 FEMALE	SEM	1.11	0.8	4,057	5.4	30.2	48.5	8.5	0.7	0.03	0.28	0.052	0.13	0.40	0.6	7.6
	P25	34.4	5.2	10,521	18.0	18.0	16.5	62.5	12.5	1.00	5.10	4.730	14.55	43.45	89.0	193.0
	MED	39.8	7.9	21,940	22.0	28.0	22.0	79.0	14.0	1.10	6.20	4.920	15.00	45.30	92.0	225.0
	P75	46.9	13.6	47,501	28.5	41.5	34.0	94.0	19.5	1.10	7.70	5.115	15.55	47.15	94.0	269.0

TABLE 7

MULTIPLE REGRESSION p-VALUES* FROM WORKING LIFETIME STUDY

	THYROID		BONE MARROW				LIVER		KIDNEY	
	FTI	TSH	HGB	HCT	WBC	PLT	SGPT	GGTP	CREAT	BUN
GROUP	0.34	0.92	0.18	0.14	**0.04**	0.17	0.82	0.81	0.77	0.33
DOSE EST	0.19	0.72	0.49	0.46	0.26	0.93	N/A	0.33	0.85	0.77
AGE	0.12	0.72	0.40	**0.05**	0.45	**0.05**	0.35	**0.05**	0.85	0.45
GENDER	0.23	0.76	**0.0001**	**0.0001**	0.90	0.06	**0.0001**	**0.0001**	**0.0001**	0.07
RACE	0.28	**0.04**	**0.02**	0.10	0.27	0.27	**0.01**	0.39	**0.001**	0.73
REF LAB	**0.0001**	0.10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*p-values for AGE, GENDER, RACE and REF LAB are the arithmetic average of p-values obtained using GROUP and DOSE EST

FIGURE 1 TSH, SINGLE SHIFT STUDY

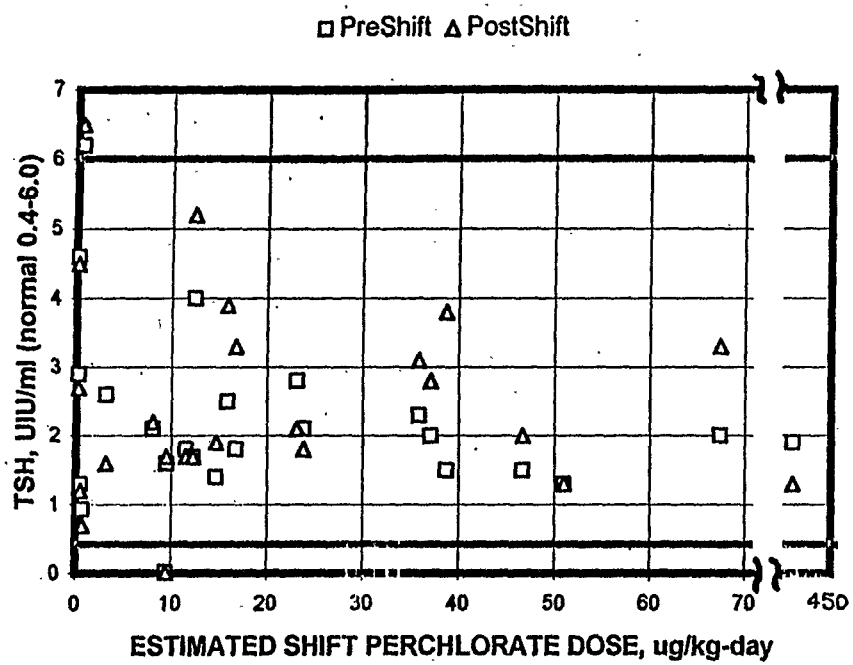

FIGURE 2 FTI, SINGLE SHIFT STUDY

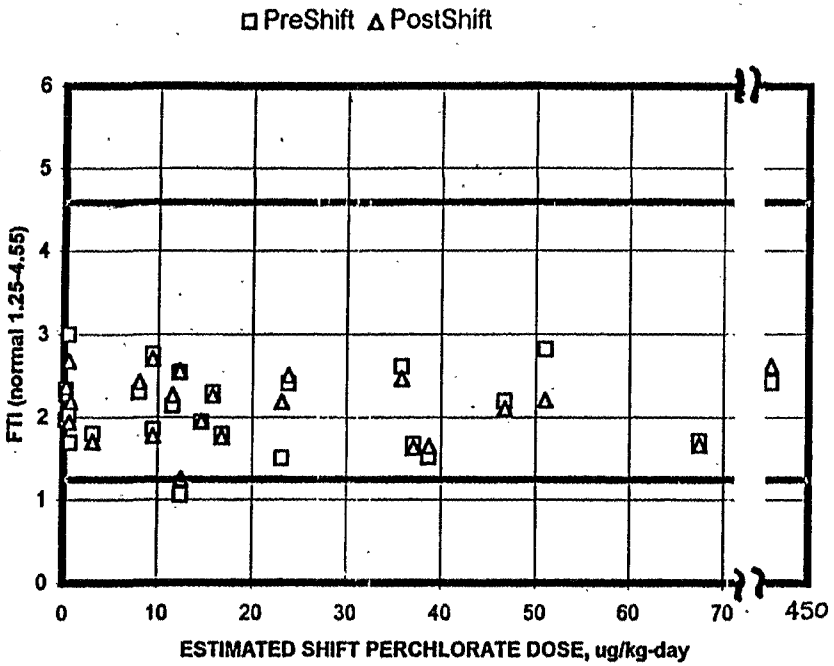

FIGURE 3 TSH, WORKING LIFETIME STUDY

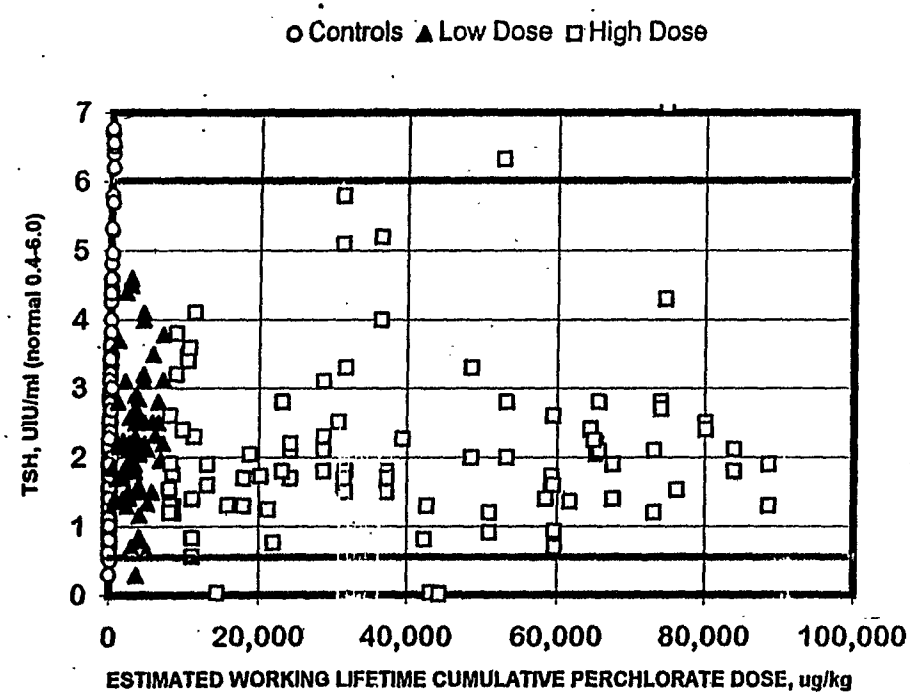

FIGURE 4 FTI, WORKING LIFETIME STUDY